

**Malattie Neurodegenerative**  
*Classificazione Clinica*

Sindromi con Progressiva Demenza

Sindromi con Disturbo della Postura e del Movimento

Sindromi con Atrofia Muscolare Progressiva

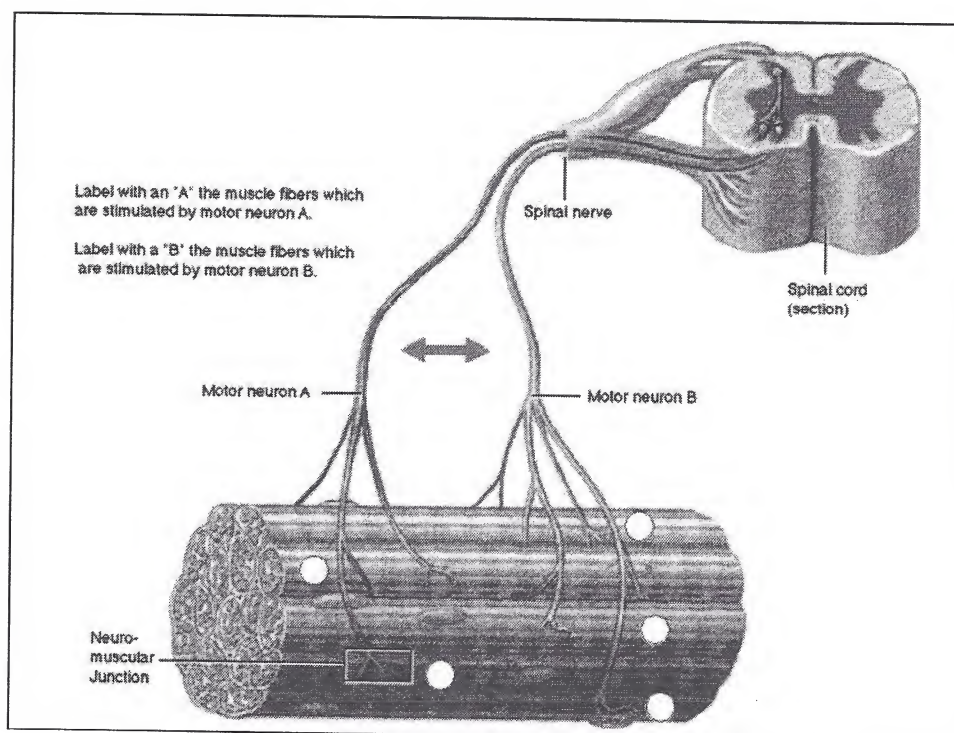
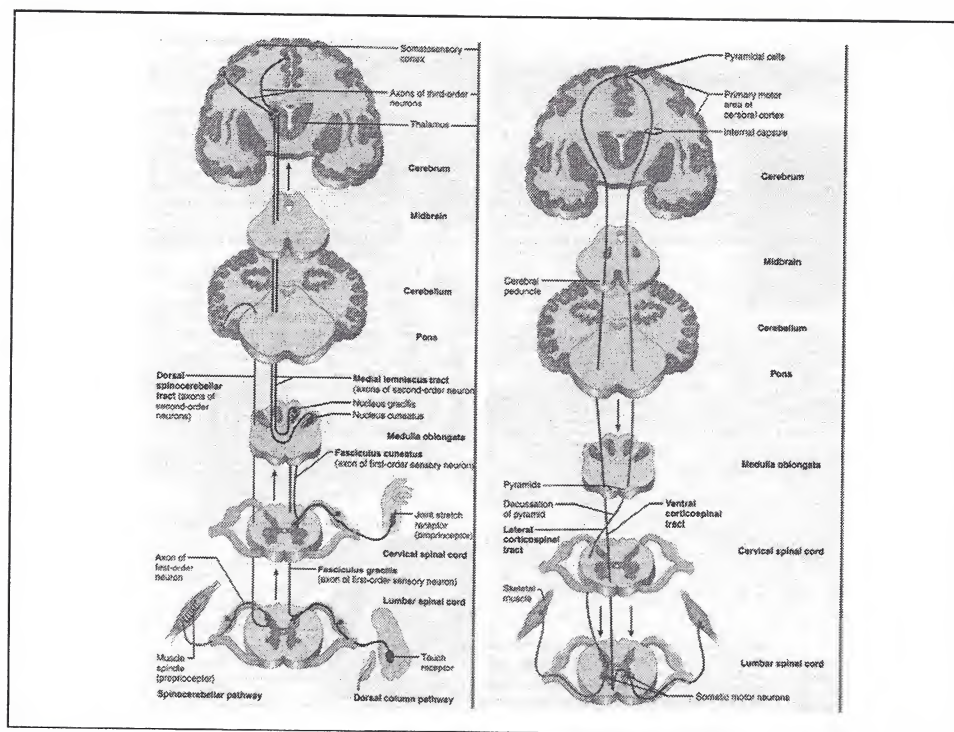
Sindromi con Paraparesi Spastica

Sindromi con Progressiva Atassia

ATROFIA MUSCOLARE SPINALE

PARAPLEGIA SPASTICA EREDITARIA

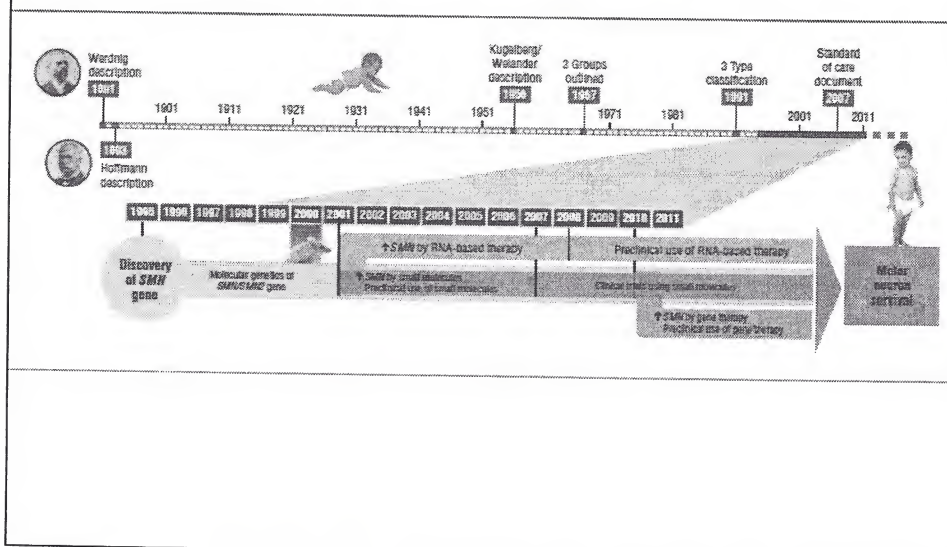
ATASSIA (SPINO-) CEREBELLARE



## LOWER MOTOR NEURON DISEASE

distal Hereditary Motor Neuropathy	AD
Spinal Muscular Atrophy	AR
Bulbar-Spinal Muscular Atrophy (X-linked)	X-linked
(Hereditary Spastic Paraplegia	AD/AR)

## SPINAL MUSCULAR ATROPHY History of the Disease



## SPINAL MUSCULAR ATROPHY

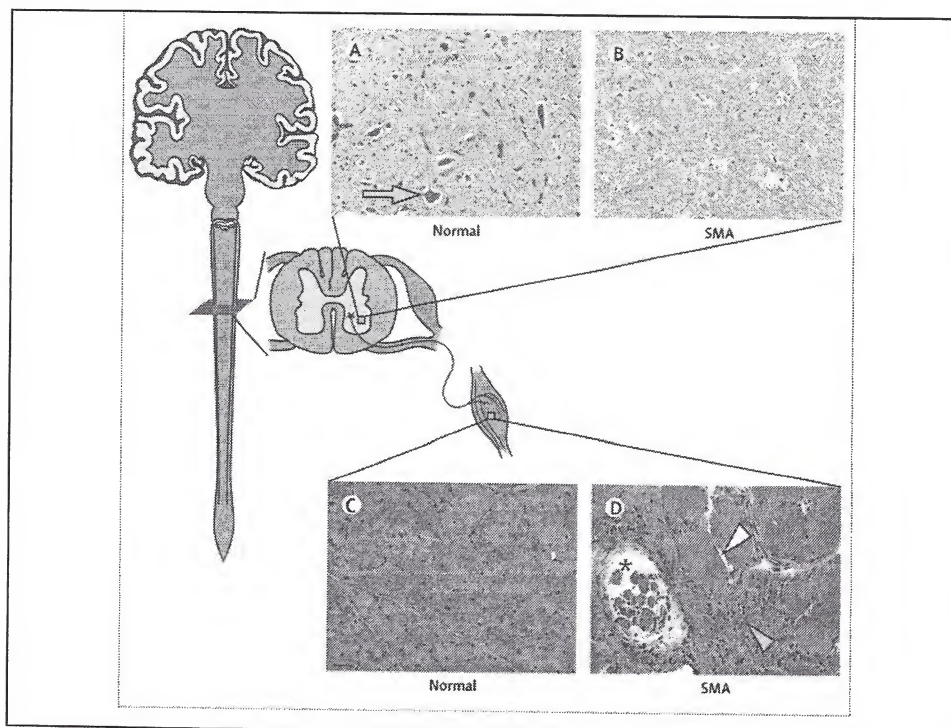
**Definition:** progressive muscle weakness from degeneration and loss of the anterior horn cells in the spinal cord and brainstem nuclei

onset from before birth to adolescence or young adulthood  
poor weight gain, sleep difficulties, pneumonia, scoliosis, joint contractures as common complications

**Incidence** 4-10/100000 live births  
Italy 7.8/100000 (1992)

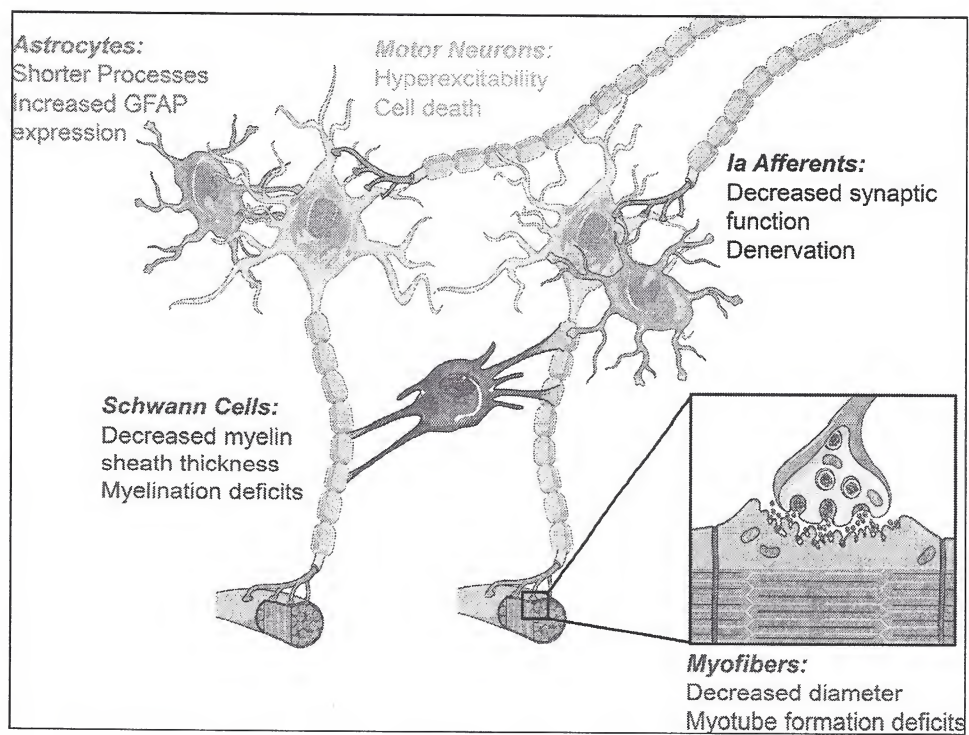
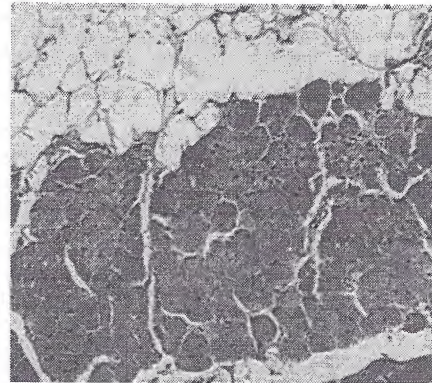
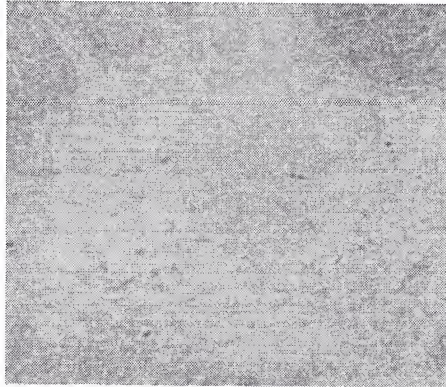
**Clinical Diagnosis:** motor difficulties  
evidence of motor unit disease

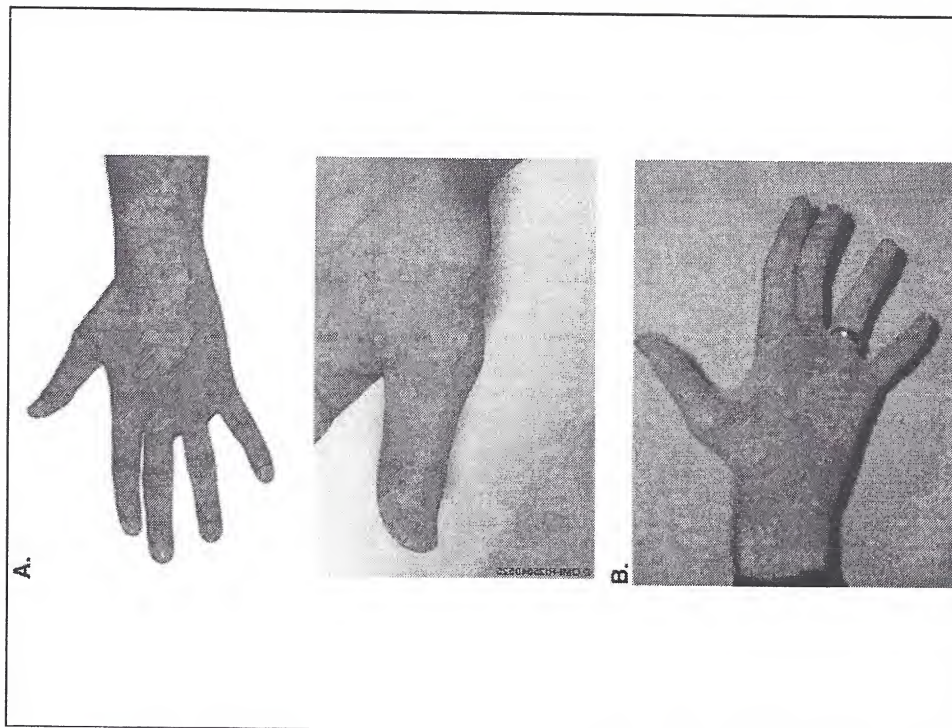
**Testing** Neurophysiology: denervation, diminished motor action potential  
Molecular Genetic: *SMN1*: homozygous deletion or truncation (95%)  
*SMN2*: 3-copies of the gene (milder forms)  
(*TK2* gene and mtDNA depletion)





## SPINAL MUSCULAR ATROPHY





### SPINAL MUSCULAR ATROPHY

	<i>onset</i>	<i>life span</i>	<i>motor milestones</i>	<i>others</i>
SMA I	<6 mos	≤2 yrs (or longer)	sit with support	mild joint contractures minimal facial weakness suck and swallow difficulties
SMA II	6-18	70% alive at 25 yrs	independent sitting	postural tremor or fingers wheel-chair bound
SMA III	>12 yrs	normal	independent ambulation	wheel-chair bound (late)
SMA IV	adulthood	normal	normal	

### "FLOPPY INFANT"



### SPINAL MUSCULAR ATROPHY

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SMA IV	adulthood	normal	normal	



## HEREDITARY SPASTIC PARAPLEGIA

### Age of Onset and Phenotypes

Congenital

Late Infantile

Childhood-Adolescence

Adulthood

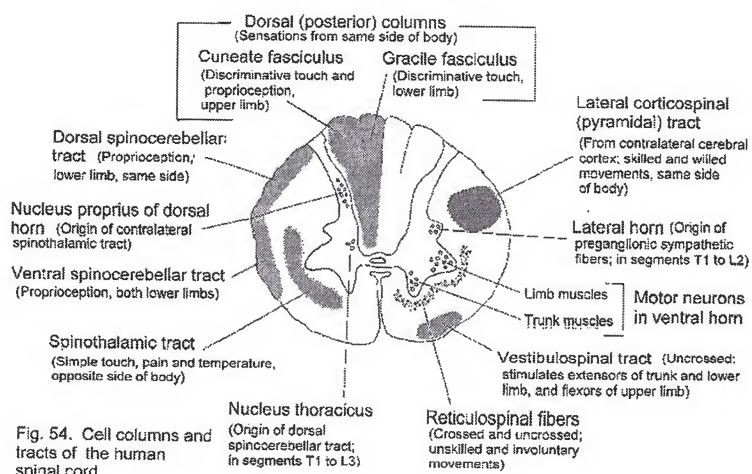
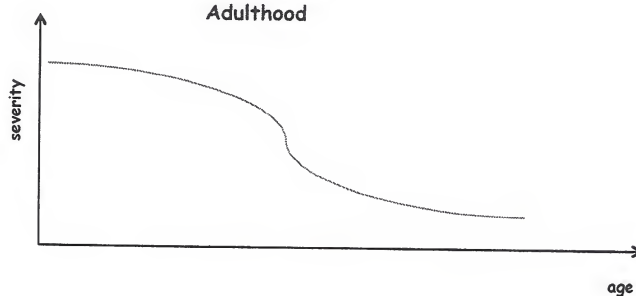


Fig. 54. Cell columns and tracts of the human spinal cord



## HEREDITARY SPASTIC PARAPLEGIA

**Definition:** insidiously progressive lower-extremity weakness and spasticity

begins at any age, from early childhood through late adulthood  
progresses slowly over many years without exacerbations, remissions

**Uncomplicated HSP ("pure")**

difficulty walking (often require canes, walkers, or wheelchairs)  
urinary urgency  
lower-extremity paresthesiae

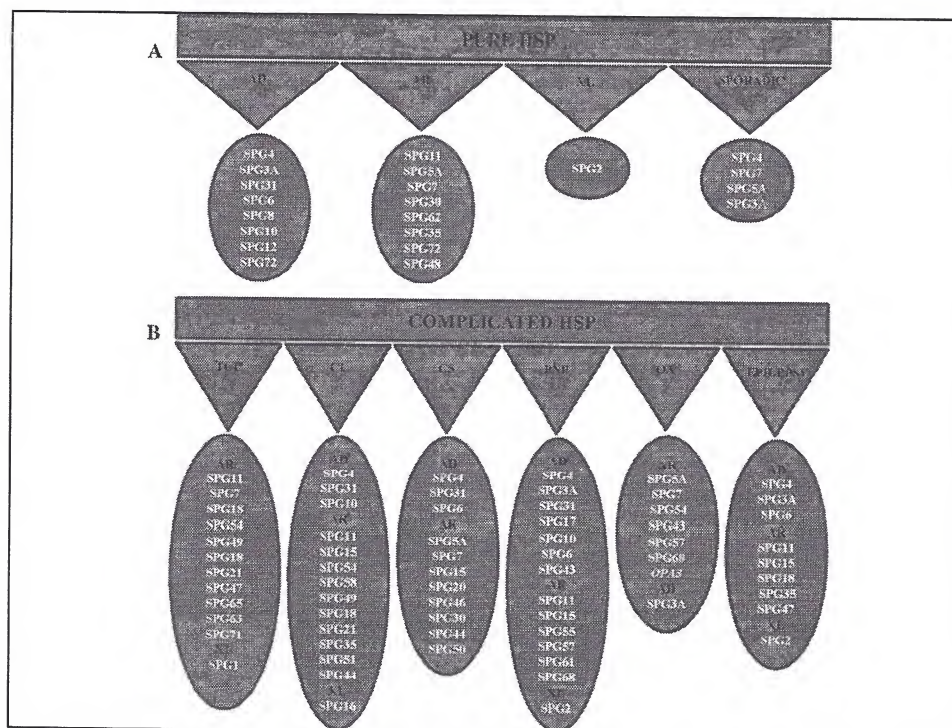
**Complicated HSP**

see above plus

other system involvement or

other neurologic findings such as seizures, mental retardation, dementia, amyotrophy, extrapyramidal disturbance, or peripheral neuropathy

Many types of complicated HSP are associated with symmetric muscle atrophy of the distal upper and lower extremities.



## HEREDITARY SPASTIC PARAPLEGIA

### Clinical Features

Bilateral lower-extremity spasticity and weakness that is maximal in the iliopsoas, hamstring, and tibialis anterior muscles.

Spasticity and weakness are variable: spasticity with no weakness,  
spasticity and weakness in approximately the  
same proportions.

Lower-extremity hyperreflexia and extensor plantar responses  
Mildly hyperactive deep tendon reflexes in the upper extremities

Mildly impaired vibration sensation in the distal lower extremities and occasionally,  
of joint position sensation

Normal strength and dexterity of the upper extremities and no involvement of  
speech, chewing, or swallowing.

## HEREDITARY SPASTIC PARAPLEGIA

### Diagnostic Criteria:

Laboratory Findings	Neurophysiology	SEP (SMC) EMG/ENG
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Neuroimaging

Inheritance	AD AR X-linked
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Genetics  
(Biochemistry)

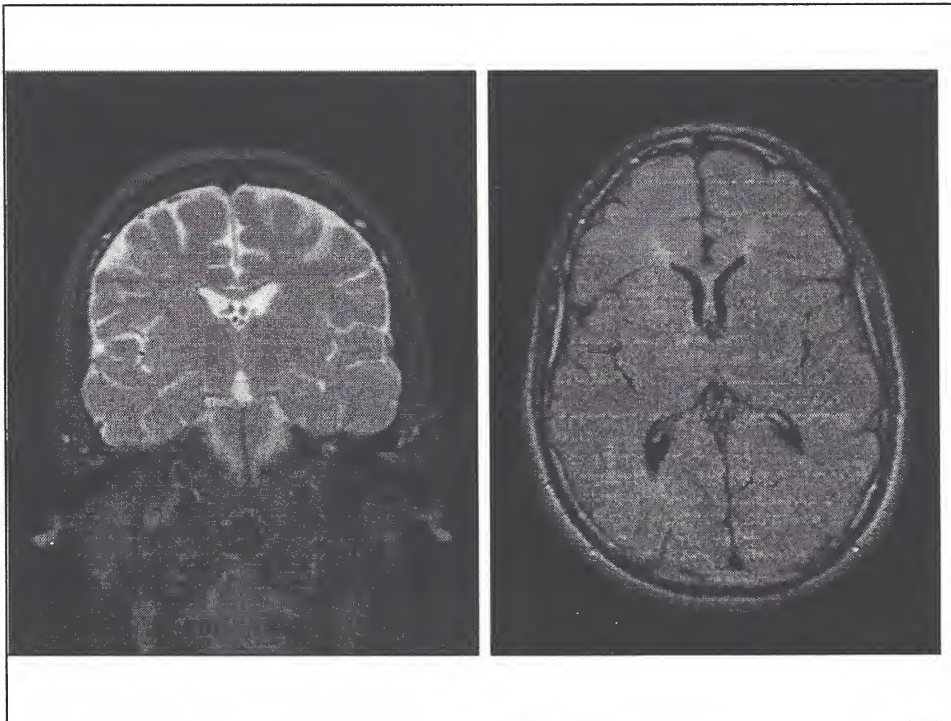
## HEREDITARY SPASTIC PARAPLEGIA

Genetics		Autosomal Dominant Forms	
SPG3A	<i>SPG3A/Atlastin</i> (GTPase similar to dynamin)	uncomplicated onset: non progressive spastic gait (DD: cerebral palsy)	childhood
SPG4	<i>Spast/Spastin</i> (Microtubule-bound protein?)	uncomplicated* complicated	3rd decade infancy-senescence
SPG10	<i>KIF5A</i> (axonal flow related protein)	(un)complicated	infancy-adulthood
SPG17	<i>BSCL2/seipin</i> (ER membrane protein)	complicated	adolescence

\* most frequent HSP

## HEREDITARY SPASTIC PARAPLEGIA

Genetics		<u>Autosomal Recessive Forms</u>	
SPG7	<i>SPG7/paraplegin</i> (proteina mitocondriale)	complicated	adulthood
SPG11	<i>SPG11/KIAA1840</i>	complicated (thin corpus callosum, MR)	child-adulthood
SPG20	<i>SPG20/spartin</i> (traffico endosomiale?)	complicated (Troyer syndrome)	childhood
SPOAN syndrome	(Spastic Paraplegia Optic Atrophy Neuropathy)	complicated	infancy



### HEREDITARY SPASTIC PARAPLEGIA

Genetics		X-linked	
SPG1	<i>LICAM*</i>	complicated	congenital
SPG2	<i>PLP1</i>	complicated	childhood
Allan-Herndon Dudley	<i>SLC16A2/</i> <i>MCT8</i>	complicated	congenital
<p>*L1 syndrome:</p> <ul style="list-style-type: none"> <li>-X-linked hydrocephalus with stenosis of aqueduct of Sylvius (HSAS)</li> <li>-Mental retardation, Aphasia, Spastic paraplegia, Adducted thumb (MASA)</li> <li>-X-linked, complicated corpus callosum agenesis</li> </ul>			

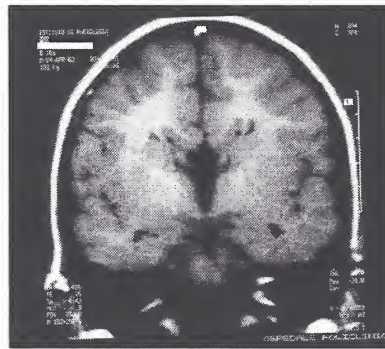


SPG1

LICAM\*

complicated

congenital



\*L1 syndrome:

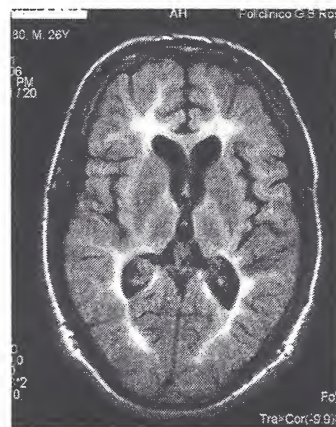
- X-linked hydrocephalus with stenosis of aqueduct of Sylvius (HSAS)
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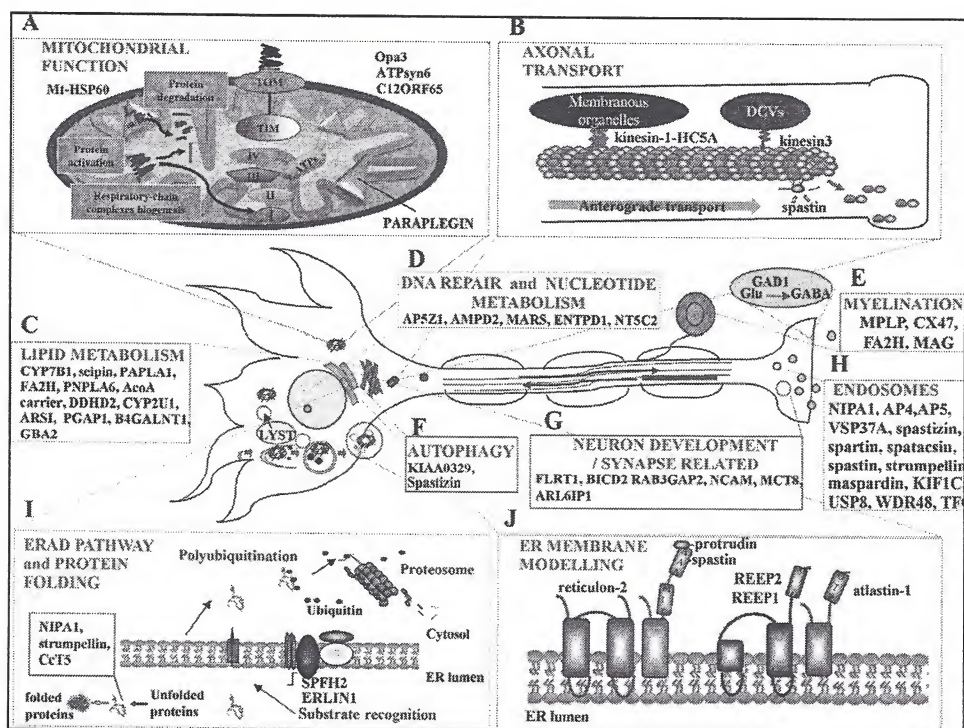
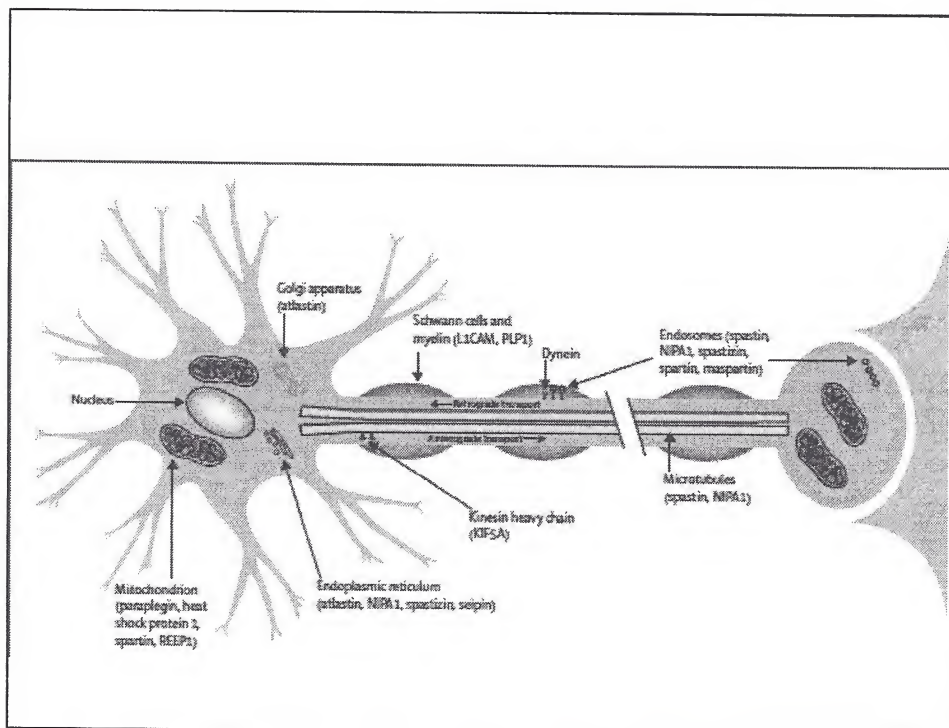
SPG2

PLP1

complicated

childhood





## INHERITED ATAXIAS

Clinical manifestations of hereditary ataxia are poor coordination of movement and a wide-based, uncoordinated, unsteady gait. Poor coordination of the limbs and of speech is often present.

Ataxia may result from dysfunction of the cerebellum and its associated systems, lesions in the spinal cord, peripheral sensory loss, or any combination of these three conditions.

Prevalence	HCA 9-11:100000 (Italy, Egypt, UK, Portugal)
	ADCA 4-5.6:100000 (Norway, Portugal, Japan)
	ARCA 2.3-5.3:100000
	FRDA 2-4:100000
	A-T 1-2.5:100000

## Cerebellar divisions

**Spinocerebellum**  
(Vermis + Intermed. Hem)

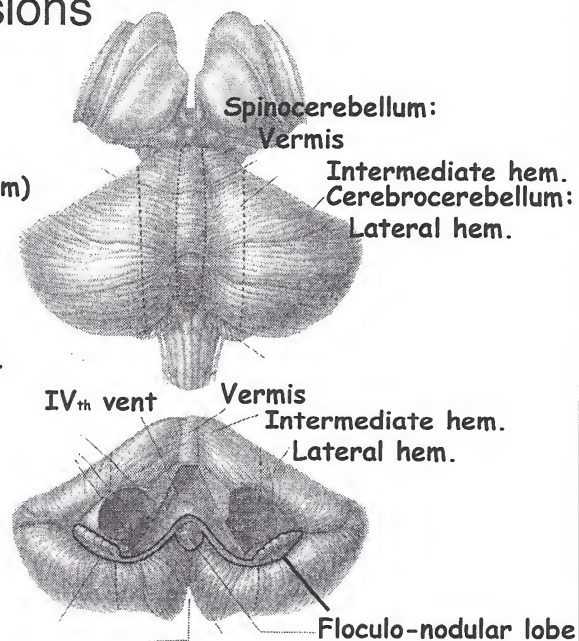
Control of limbs  
and trunk

**Cerebrocerebellum**  
(Lateral hemisphere)  
Planning of movement+

**Vestibulo-cerebellum**  
(Floculo-nodular lobe)

Control of eye &  
head movements  
Balance

NTA Fig. 13-1



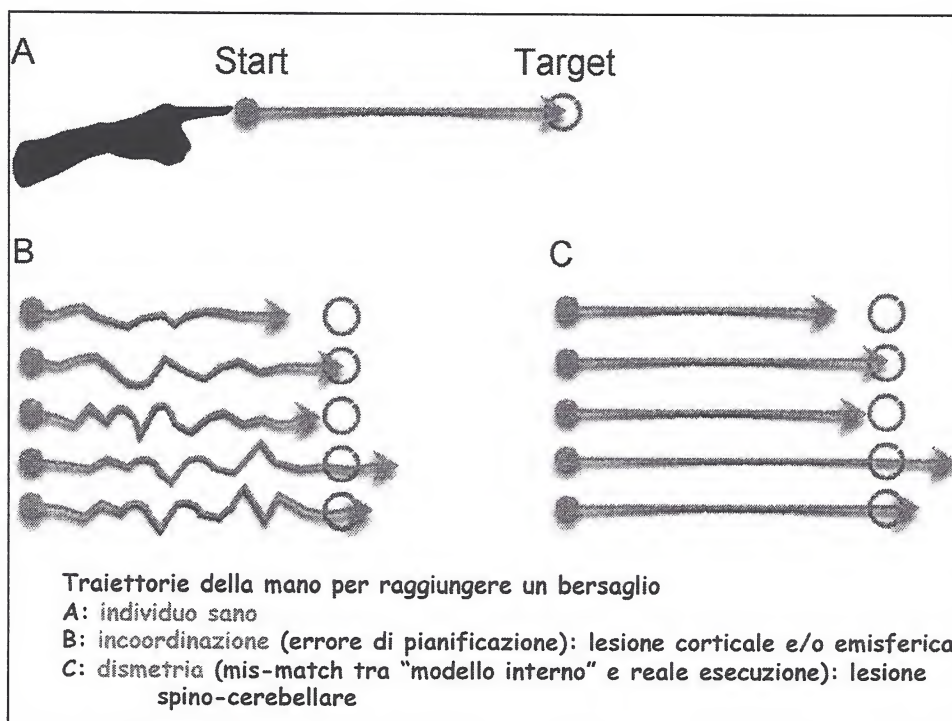
## Principali Segni e Sintomi di Coinvolgimento Cerebellare

Incoordinazione del Movimento Volontario  
 della muscolatura degli arti    atassia  
 della muscolatura orale        disartria  
 (della MOE coniugata)        nistagmo

Tremore "Intenzionale"

Disturbo dell'Equilibrio (Marcia), della Stazione Eretta

Riduzione del Tono Muscolare



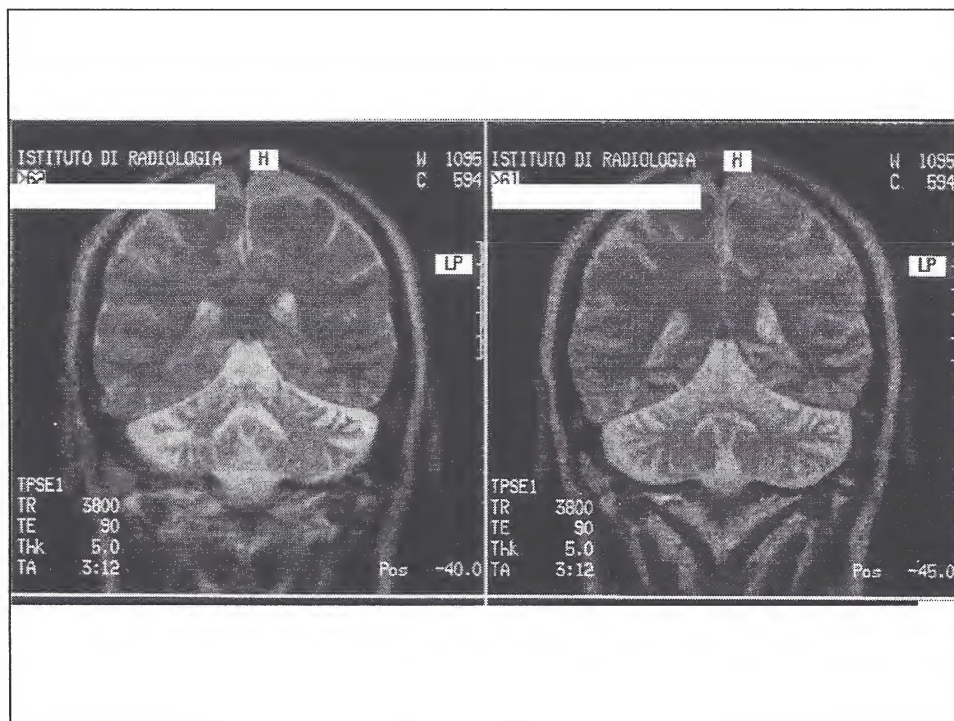


## Autosomal Dominant Cerebellar Ataxias

ADCA Type I	cerebellar and non-cerebellar signs (SCA1-4, SCA8, SCA10, SCA12-23, SCA25, SCA27, SCA28, SCA32-36)
ADCA Type II	as above plus pigmentary maculopathy (SCA7)
ADCA Type III	pure (+ non cerebellar signs: pyramidal signs, parkinsonism, neuropathy (SCA30-31)

## Autosomal Dominant Cerebellar Ataxias

				cerebellar ataxia associated with
SCA1 (I)	ATXN1	CAG repeat	3rd-4th	pyramidal signs, peripheral neuropathy
SCA2 (I)	ATXN2	CAG repeat	3rd-4th	slow saccades, peripheral neuropathy, dementia
SCA3 (I)	ATXN3	CAG repeat	4th	pyramidal extra-pyramidal signs, nystagmus, slow saccades, amyotrophy, fasciculations, sensory loss
SCA6 (III)	CACNA1A	CAG repeat	5th-6th	episodic ataxia, slow progression
SCA7 (II)	ATXN7	CAG repeat	3rd-4th	visual loss with retinopathy
DRPLA	ATN1	CAG repeat	3rd-4th	chorea, seizures, myoclonus
EA1	KCNA1	mutations	1st decade	myokymia (induced by activity; no vertigo)
EA2	CACNA1A	mutations	1st decade	attacks of long lasting nystagmus (postural changes)-->permanent ataxia; vertigo
ADSA	SAX1	mutations	1st decade	progressive leg spasticity, peripheral neuropathy



### Autosomal Recessive Cerebellar Ataxias

			cerebellar ataxia associated with
FRDA	<i>FXN</i>	GAA triplet expansion	1st decade sensory neuropathy; amyotrophy; Babinski sign; dysarthria; cardiomyopathy
AVED	<i>TTPA</i>	mutations	8-15 yrs sensory neuropathy, dysarthria, dystonia, mental decline, psychosis, retinopathy, head titubatio
ARSACS	<i>SACS</i>	mutations	1st decade spasticity, peripheral neuropathy, retinal striation
A-T	<i>ATM</i>	mutations 7:14 translocation	1-4 yrs choreoathetosis, oculomotor apraxia, telangectasia
AOA1	<i>APTX</i>	mutations	childhood oculomotor apraxia--> ophthalmoplegia, mild MR, choreoathetosis, severe motor neuropathy
AOA2	<i>SETX</i>	mutations	2nd decade oculomotor apraxia, sensorimotor neuropathy
MSS	<i>SIL1</i>	mutations	congenital mental retardation, myopathy, cataract, short stature
IOSCA	<i>PEO1</i>	mutations	infantile athetosis, ophthalmoplegia, optic atrophy, neuropathy
Refsum d	<i>PHYH/PEX7</i>	mutations	1-6th dec neuropathy, deafness, ichthyosis, retinopathy

Table 3. Clinical Features, Laboratory and Brain MRI Findings, and Molecular Features of the Major Autosomal Recessive Cerebellar Ataxias. <sup>a</sup>					
Disease	Age at Onset yr	Clinical Features	Laboratory Findings	Brain MRI Findings	Gene and Protein
<b>Cerebellar ataxia with pure sensory neuropathy</b>					
Friedreich's ataxia	Mean, 16; 7–25 in most cases; reported range, 2–60	Most frequent recessive ataxia; bilateral extensor plantar reflexes; scoliosis; square-wave jerks	GAA triplet repeat expansion in intron 1 of the FXN gene	No cerebellar atrophy; spinal cord atrophy	FXN, frataxin
Sensory axonal neuropathy with dysarthria and ophthalmoplegia	Range, 20–60	Ophthalmoparesis; dysarthria; ptosis; myoclonus	Variable elevation of serum lactic acid level	Variable cerebellar atrophy; cerebellar white-matter changes; stroke-like lesions	POE, polymerase gamma
Ataxia with vitamin E deficiency	Mean, 17; range, 2–50	Similar to Friedreich's ataxia; retinitis pigmentosa; variable head tremor	Significantly decreased serum vitamin E level†	No cerebellar atrophy; spinal cord atrophy	TTPA, alpha-tocopherol transfer protein
Abetalipoproteinemia	Birth	Vomiting; diarrhea; neonatal steatorrhea	Decreased serum levels of cholesterol, triglycerides, and vitamins A, D, E, and K; abetalipoproteinemia; acanthocytosis	No cerebellar atrophy	MTP, microsomal triglyceride transfer protein
<b>Cerebellar ataxia with sensorimotor axonal neuropathy</b>					
Ataxia telangiectasia	Range, 2–3; <5 in most cases	Telangiectasias; oculocephalic dissociation; susceptibility to infections and cancer; chorea, dystonia, or both	Elevated serum alpha-feto-protein level; immunoglobulin deficiency; mosaic translocations (specific karyotype)†	Cerebellar atrophy	ATM, ataxia telangiectasia mutated
Ataxia with oculomotor apraxia type 1	Mean, 7; range, 1–20	Variable oculocephalic dissociation; chorea, dystonia, or both	Variable elevation of serum LDL cholesterol level and low serum albumin level	Cerebellar atrophy	APTX, aprataxin
Ataxia with ocular apraxia type 2	Mean, 15; range, 7–25	Variable oculocephalic dissociation; chorea, dystonia, or both	Elevated serum alpha-feto-protein level†	Cerebellar atrophy	SETX, senataxin

Late-onset GM <sub>2</sub> gangliosidosis	Range, 15–45	Spasticity, weakness, dystonia, epilepsy, cognitive decline, psychosis, anterior horn involvement	Hexosaminidase A deficiency (late-onset Tay-Sachs disease); hexosaminidase A-B deficiency (Sandhoff's disease)	Cerebellar atrophy	HEXA (Tay-Sachs variant) or HEXB (Sandhoff's disease variant)
Congenital disorder of glycosylation type 1A	Birth	Mental retardation; retinitis pigmentosa; thoracic deformity; epilepsy	Serum transferrin isoelectric focusing	Cerebellar atrophy	PMM2, phospho-mannomutase
Autosomal recessive spastic ataxia of Charlevoix-Saguenay	Mean, 2; up to 12	Spastic paraparesis followed by spastic ataxia; demyelinating component of the neuropathy; hypertrophy of the myelinated fibers [of the fundus]		Anterior superior cerebellar atrophy; variable T <sub>2</sub> -weighted linear hypointensities in pons	SACS, sacsin
Refsum's disease	Range, 10–20	Retinitis pigmentosa; sensorineural deafness; demyelinating neuropathy	Elevated serum phytanic acid level†	No cerebellar atrophy	PHYH, phytanoyl-CoA hydroxylase and PEX7
Cerebrotendinous xanthomatosis	Childhood	Spastic ataxia; mental retardation, dementia, or both; tendon xanthomas; chronic diarrhea; premature cataracts	Elevated serum cholesterol level†	Variable cerebellar atrophy; cerebellar or cerebral leukodystrophy	CYP27, sterol 27 hydroxylase
<b>Cerebellar ataxia without neuropathy</b>					
Autosomal recessive cerebellar ataxia type 1	Late onset; mean, 32; range, 17–46	Pure ataxia	Not applicable	Cerebellar atrophy	SYNE1, spectrin repeats-nuclear envelope 1
Autosomal recessive cerebellar ataxia type 2	Mean, 4; range, 1–11	Mental retardation, myoclonus, epilepsy, stroke-like condition, exercise intolerance	Variable elevation of serum lactic acid level and decreased coenzyme Q10 level	Cerebellar atrophy; variable stroke-like cerebral lesions	ADCK3 (CABC3), sarf-domain containing kinase 3
Niemann-Pick type C disease	Range, 2–30	Vertical supranuclear ophthalmoplegia, splenomegaly, dystonia, cognitive disorder	Skin-biopsy findings (filipin staining)	Variable cerebellar or brain atrophy	NPC1, NPC1 and NPC2, NPC2

Table 2. Typical Signs and Symptoms of a Cerebellar Ataxia and Mistakes to Avoid if the Diagnosis of Cerebellar Ataxia Is Uncertain.	
<b>Typical signs and symptoms of cerebellar ataxia</b> Clumsiness, swerving Difficulty in walking Balance problems, swaying, falling (leading to or manifested as trauma) Difficulty in dressing, handling utensils, and writing Slurred speech Hypotonia, slowness Delayed motor development (onset of walking after 18 mo) Intentional hand tremor Dizziness (patient is sometimes referred to otorhinolaryngologist) Visual disturbances (patient is sometimes referred to ophthalmologist) Incidental finding of cerebellar atrophy on magnetic resonance imaging	
<b>Mistakes to avoid if diagnosis of cerebellar ataxia is uncertain</b> Neglecting the disorder Considering a psychiatric origin Suspecting an otorhinolaryngologic, ophthalmologic, orthopedic, or a rheumatologic cause Not requesting a second examination several weeks or months later Not referring patient to a neurologist or a pediatrician who specializes in neurology Not urgently investigating an acute cerebellar ataxia	

## MALATTIA di FRIEDREICH

### Criteri Diagnostici

#### *essenziali* (entro 5 anni dall'esordio)

esordio entro i 25 aa  
ataxia progressiva degli arti e della marcia  
risposta plantare estensoria  
assenza riflessi profondi degli arti inferiori  
MNCV >40 m/s con SAP ridotto o assente

#### *aggiuntivi*

scoliosi  
segni piramidali degli arti inferiori  
assenza riflessi profondi arti superiori  
disturbi sensibilità profonda degli arti inferiori  
alterazioni ECG

50% dei pazienti possono presentare

nistagmo  
atrofia ottica  
sordità  
amiotrofia distale  
piede cavo  
diabete



## MALATTIA di FRIEDREICH

### Genetica e Patologia

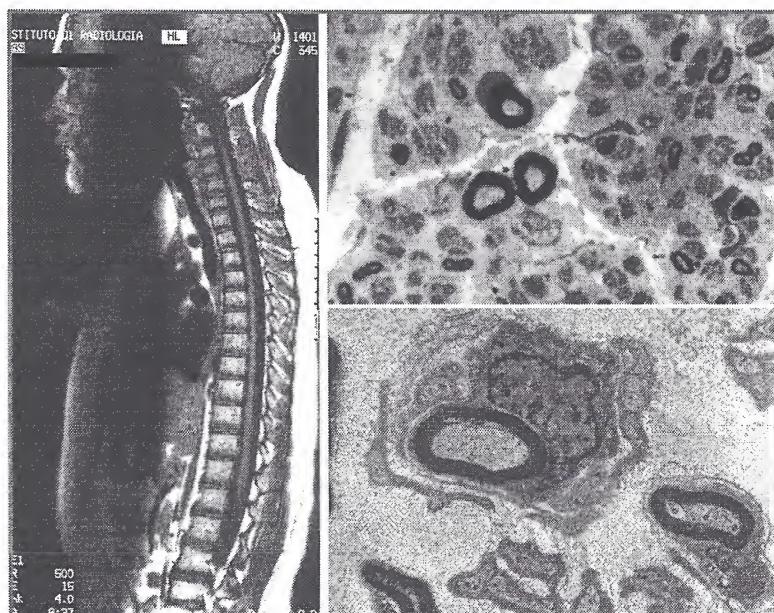
prevalenza 2/100000

cromosoma 9q GAA repeats intronici  
95% omozigosi  
5% repeats/mutazioni puntiformi

*fratassina*: proteina mitocondriale, deputata alla produzione della energia cellulare

interessamento sistemi di fibre che si originano da:  
neuroni gangli spinali  
motoneuroni  
neuroni piramidali motori

FRDA FXN GAA triplet expansion 1st decade sensory neuropathy; amyotrophy; Babinski sign; dysarthria; cardiomyopathy



## ATASSIA SPASTICA FAMLIARE

15 mesi: inizio deambulazione

II anno: atassia AAI

4 aa: atassia della marcia con ipotonia; note di steppage; iporeflessia achillea;  
ritardo linguaggio

7 aa: marcia parapareto-atassica; clono bilaterale del piede con segno di Babinski;  
rr profondi presenti; ipopallestesia distale AAI

SMC: conduzione centrale

SEP: ↓↓ conduzione centrale

BAERS: ↓ non valutabile la componente centrale

RMN-encefalo: atrofia cerebellare

Analisi Molecolare gene SACS: mutazione in eterozigosi

2343insT  
R895X

ARSACS SACS mutations

1st decade spasticity, peripheral neuropathy,  
retinal striation



## ATASSIA SPASTICA FAMLIARE

